BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

The Patent Office

INVESTOR IN PEOPLE

GB99/511

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP9 1RH

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

PRIORITY DOCUMENT

SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Signed Andrew Gersey

Dated 2 March 1999

al use

19FEB98 E339575-1 D03312
P01/7700 25.00 - 9803448.1

18 FEB 1998

Your reference 230P78531

9803448.1

Notes
Please type, or write in dark ink using CAPITAL letters. A prescribed fee is payable for a reques for grant of a patent. For de ls, please contact the Patent Office (telephone 071–829 6910).

Rule 16 of the Patents Rules 1990 is the main rule governing the completion and filing of this form.

② Do not give trading styles, for example, 'Trading as XYZ company', nationality or former names, for example, 'formerly (known as) ABC Ltd' as these are not required.

THE PATENT OFFICE
A
18 FEB 1998
LONDON

Warning
After an application for a Patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977 and will inform the applicant if such prohibition or restriction is necessary. Applicants resident in the United Kingdom are also reminded that under Section 23, applications may not be filed abroad without written permission unless an application has been filed not less than 6 weeks previously in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction revoked.

The Patent Office

Request for grant of a Patent
Form 1/77

Patents Act 1977

① Title of invention

1 Please give the title of the invention

Pharmaceutical Formulation

② Applicant's details

☐ **First or only applicant**

2a If you are applying as a corporate body please give:

Corporate name: Pharma Mar, S. A.

Country *(and State of incorporation, if appropriate)*:

2b If you are applying as an individual or one of a partnership please give in full:

Surname:

Forenames:

2c **In all cases**, please give the following details:

Address: Calle de la Calera, 3,
Poligono Industrial de Tres Cantos
28760 Tres Cantos, Madrid, Spain

UK postcode *(if applicable)*:

Country:

ADP number *(if known)*: 4351 41003

eference number

4 Agent's or applicant's reference number *(if applicable)* 230P78531

⑤ Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No ☒ ➡ ***go to 6***

⬇

please give details below

☐ number of earlier application or patent number

☐ filing date

(day month year)

☐ and the Section of the Patents Act 1977 under which you are claiming:

Please mark correct box

15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

⑥ Declaration of priority

⑥ If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number *(if known)*	Filing date *(day, month, year)*

Document #: 234558

PHARMACEUTICAL FORMULATION

The present invention relates to a pharmaceutical formulation, and more particularly a pharmaceutical formulation of a didemnin.

THE BACKGROUND

US Patent 5,294,603 to Rinehart claims a pharmaceutical composition comprising a didemnin, in combination with a pharmaceutically acceptable carrier, excipient or diluent. In that patent, extensive results are given for testing for biological activity, notably assay results for cytotoxicity and antiviral activity. No examples are provided of the claimed pharmaceutical composition and no information is given regarding the identity of the pharmaceutically acceptable carrier, excipient or diluent.

THE PROBLEM

In practice, there are some difficulties in preparing pharmaceutical compositions of didemnins suited for administration to patients, and especially a need for a stable parental pharmaceutical dosage form.

THE INVENTION

The present invention provides a pharmaceutical composition of a didemnin, comprising firstly a lyophilised didemnin preparation and secondly a reconstitution solution.

surfactant is suitably 10 to 25 % v/v of the mix; the alkanol is suitably 10 to 25 % v/v of the mix; and the water is suitably 50 to 80 % v/v of the mix.

EXAMPLES

Freeze-drying was performed from a 1.0 mg/ml solution aplidine in 40% v/v t-butanol in water for injection ("WFI") containing 25 mg/ml mannitol as bulking agent. Differential scanning calorimetry studies were conducted to determine the freeze-drying cycle parameters. The prototype, containing 1.0 mg aplidine and 25 mg mannitol per vial was found to be the optimal formulation in terms of solubility, length of the freeze-drying cycle and dosage requirements.

A solution composed of 15/15/70% (v/v/v) Cremophor EL/ethanol absolute/WFI was found to be the optimal reconstitution solution, Cremophor EL being a glycerol-polyethylene glycol ricinoleate available from BASF in Germany.

Dilutions of reconstituted product with normal saline up to 1:200 showed it to be stable for at least 24 hours after preparation. Quality control of the freeze-dried formulation demonstrated that the manufacturing process does not change the integrity of aplidine. Shelf-life data, available thus far, show that the formulation is stable for at least 6 months when stored at +4°C in the dark.

Thus, the preferred aplidine product of this invention is a dual-package containing:

an injection vial containing aplidine 1 mg/vial lyophilized product, and

an injection vial containing 2 ml of 15/15/70% (v/v/v) Cremophor EL/ethanol/water as reconstitution solution.